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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2005D-0062; Draft Guidance on FDA's "Drug Watch" for Emerging Drug Safety Information (70 Federal Register 24606; May 10, 2005)

Dear Sir/Madam:

GlaxoSmithKline (GSK) is a research-based pharmaceutical company engaged in the discovery, development, manufacture, and sale of prescription and over-the-counter pharmaceutical products, vaccines, and over-the-counter devices. GSK supports the Agency's ongoing efforts to improve risk communication, and we appreciate the opportunity to provide comments on the draft *Guidance on FDA's "Drug Watch" for Emerging Drug Safety Information.*

As noted in the draft guidance, FDA has a long history of providing information on drug benefits and risks to healthcare professionals and patients when that information has generated a specific concern or prompted a regulatory action such as a labeling change. The proposed Drug Watch Web page would make emerging drug safety information available to the healthcare community, patients and other stakeholders in a new format and earlier than in the past, while the issue is still under active review by the Agency and sponsor. GSK supports the Agency's efforts to increase transparency in establishing the benefits and safety profiles of drug products and in communicating potential safety concerns to relevant stakeholders in an appropriate and timely manner. However, we have a number of concerns and questions regarding the content of the draft guidance document, and the Drug Watch program itself, including the information to be included in the Drug Watch postings, and potential unintended consequences that may result from misinterpretation of preliminary safety information.

Our major concerns include:

- *Public health impact of Drug Watch information:* The draft guidance document does not address the public health consequences of posting emerging drug safety issues to the Drug Watch Web site. The document should consider how FDA can best inform and involve the medical community to ensure physicians are not surprised by patients' questions about posted information the physician is unaware of and to minimize the chances that patients will draw inappropriate conclusions – possibly jeopardizing their health – based on a misunderstanding of emerging data. This outcome could have far greater impact on public health than any risk from the unsubstantiated signal. The posting should indicate, for example, whether or not any specific action is recommended on the part of physicians and/or patients.

  Although the intent of providing early notice of emerging safety issues has merit, it is important to consider the limited capabilities of many consumers to make informed decisions about managing their own healthcare or deciding to seek professional advice. Similarly, despite the disclaimers regarding the preliminary nature of the information, the mere fact of its posting on the Drug Watch Web page may drive some physicians to discontinue treatment for fear of litigation. Alternative medications which may be prescribed, while not on the Drug Watch Web page, could

have more common, or more serious adverse events than those potential risks of the product on the Drug Watch page. It is therefore critical to explain in detail not only the ambiguous nature of an emerging safety issue, but also the offsetting benefits of continued drug use, the comparative risks of discontinuing medication (either with or without a physician's consent), and the range of possible treatment alternatives.

- *Possible unintended negative consequences:* In addition to the potential impact on public health, we are also concerned that posting preliminary information on the Drug Watch Web page may have an unintended negative effect on the ability of FDA and the sponsor to further investigate the potential safety signal. Spontaneous adverse event reporting will inevitably be stimulated by the Drug Watch posting and subsequent media attention, which could result in a "self-fulfilling prophecy" in terms of signal confirmation. If the event in question is relatively commonly observed as background in a target population, this stimulated reporting could obscure any true signal. In addition, publicity surrounding the event could hamper enrollment into prospective epidemiologic and clinical studies (including those for new indications).

- *Wider impact of Drug Watch postings:* The Agency needs to consider the global impact of FDA public statements posted on their website, which are rapidly cascaded around the globe to health authorities and the media. FDA should take measures to communicate the objectives and procedures for the Drug Watch program to international health authorities. Publicizing unvalidated safety signals is a new concept, and its acceptance and interpretation will vary widely in other cultures. We believe the Agency should work closely with other health authorities so they can prepare themselves to handle local public responses to FDA Drug Watch postings. In jurisdictions where regulatory authorities are subject to parliamentary scrutiny, they may need to be prepared at short notice to justify their own position on the potential safety concern.

- *Involvement of sponsors before posting information:* Sponsors should be consulted at the time FDA is conducting their preliminary analysis, and given a defined period of time (e.g., 72 hours) to provide any additional information that may help to clarify the safety signal in question. Sponsors could also use this time to complete a preliminary evaluation, and to confirm that the information is credible. This period of time will also allow sponsors to prepare for the announcement of the emerging safety issue on the Drug Watch web site. Additional detailed comments on this point are contained in our comments on specific sections of the draft guidance document below.

- *Need for clear, well-defined and consistently applied criteria for posting and removing products from Drug Watch:* The criteria for posting information on the Drug Watch web page need to be more explicitly defined. This is particularly important because the information will be posted "before (FDA) has fully determined its significance". Given the risk of premature and/or inaccurate posting of information that could lead to confusion among healthcare providers and patients, it is crucial to have clearly defined parameters for the selection of information to be posted, including meaningful quality control measures. Similarly, the section of the document dealing with removing a product from the Drug Watch web site should provide more definitive criteria for removal, and a description of how they will be applied.

- *Impact of Drug Watch postings on labeling and litigation:* Although Drug Watch postings are intended to be a "heads up" to health care professionals, in today's litigious medical environment it is almost certain that Drug Watch warnings will be used by plaintiff's attorneys as "proof" of material safety risks, and courts may allow the warnings in such government-sponsored postings as evidence of causation. For example, a recent FDA public health advisory for pimecrolimus and tacrolimus is reportedly a model for future Drug Watch updates. Despite the preliminary nature of the potential cancer risk described in the notification, several plaintiffs' attorneys have established web sites for plaintiff recruitment, citing the advisory as proof of a causal relationship. Juries are unlikely to appreciate the complex distinctions between a Drug Watch alert and other forms of regulatory action. Due to complex jurisdictional and pre-emption issues related to

product liability actions, in the absence of additional federal legislative action, even if very clear and definitive disclaimer language is included in the final guidance document and on the Drug Watch Web page, the proposed Drug Watch program will raise significant issues related to liability exposure.

Fear of litigation could also lead to physicians practicing defensive medicine based on unvalidated safety signals, an outcome that is not necessarily in the best interest of patients. It is also possible that some sponsors, in defense of possible litigation, may elect to make labeling changes on the basis of a Drug Watch posting. If the ultimate decision is that there is no new safety concern, and the information is removed from the Drug Watch web site, the labeling could contain inappropriate precautions that could limit patient access to the benefits of drug treatment. Both litigation and labeling concerns highlight the importance of posting a clear and publicly evident notice regarding previous alerts, indicating that further investigation of the emerging safety concern revealed it to be unfounded. We suggest that the Drug Watch Web page have a prominent link to "Drugs that have been removed from Drug Watch," which would contain information on how the original concern was resolved.

Specific Comments on the Draft Guidance Document

I. Introduction

Various terms such as "important emerging safety information", "early safety signals", "potential safety issues", "emerging risks", "potential safety risks", "drug risk information", and "significant emerging safety issues", are used interchangeably throughout the document. However, these terms are not synonymous, and could potentially cause different levels of alarm, particularly to those who are not drug safety professionals. We recommend that the Agency choose one of these terms (we prefer "important emerging safety information"), define it clearly, and use it consistently, not only throughout the guidance document, but also in the Drug Watch postings. To the extent possible, the definition should match the definition of "important drug safety issue" as defined in MaPP 4151-3 on the Drug Safety Oversight Board.

On line 38, we suggest that the word "identified" be replaced by "described", as use of the word "identified" might lead the reader to think that the safety issue has been confirmed.

II. Background

The last sentence in this section (lines 64-68) notes that the FDA's goal with the Drug Watch is to share emerging safety information at an early stage "...so that patients and healthcare professionals will have the most current information concerning ***the potential risks and benefits*** of a marketed drug product upon which to make individual treatment choices." However, there is no mention in this section, or anywhere else in the draft guidance document, regarding inclusion of information about product benefits in the Drug Watch postings. The lack of balancing positive information, such as the approved indications, or other benefits for physicians or patients to consider, could negatively affect treatment decisions, especially for serious diseases. We suggest that Drug Watch entries include not only a description of the emerging safety information, but also the offsetting benefits of continuing drug use, the comparative risks of discontinuing medication, and the range of possible treatment alternatives. This information will better enable patients and their healthcare providers to make informed decisions concerning treatment.

III. Discussion

A. What information will be posted?

We suggest the FDA avoid use of the words "associated with" when describing adverse events that are still under evaluation (as in line 81), as this could be interpreted to mean that a causal relationship has already been established.

There seems to be some inconsistency between the general inclusion criteria for Drug Watch (significant emerging safety information) and the examples provided in this section, particularly examples B and C. These examples discuss risks for which a conclusion appears to have been established, rather than emerging safety risks. Specifically, the situations described in lines 96-98, "...risks that FDA believes may be associated with a drug...avoided by appropriate patient selection, monitoring..." and in lines 108-110, "...can cause liver damage. The sponsor has advised prescribers to check a patient's liver enzymes..." appear to be information that would more appropriately be included in a product's labeling. Presenting warning information on one single aspect of a drug in isolation may detract from consideration of the full set of warnings and precautions contained in the product's labeling, as well as consideration of the approved indications, which are important to any individual prescribing decision. It may be useful to provide a link to the approved labeling for the product, so that physicians and other healthcare providers have ready access to the complete prescribing information.

In addition, this section states that Drug Watch will provide information about drugs with ***significant*** emerging safety issues (line 76), but other parts of the document indicate that the aim of the program is in part to determine if emerging safety issues are, in fact, significant at all.

These contradictions and ambiguities generate uncertainty over the range of situations which FDA plans to include on the Drug Watch Web page.

With regard to the disclaimer that FDA plans to add to information that is still being evaluated (lines 120-124), we suggest that the disclaimer be expanded to include a statement that a causal relationship has not been established, and that the validity of the information is subject to verification. In addition, we request that the disclaimer specifically state that the information is not considered sufficient to warrant a change in the product's labeling. The Drug Watch web site should also include an explanation noting that posting of information about a product does not mean that the manufacturer is required to take any specific action related to the posted information.

In the Introduction section of the draft guidance document, FDA states that they intend to work "as quickly as possible to assess and address the potential safety issues..." (lines 37-38), and lines 130-131 indicate that FDA intends to update information on the Drug Watch frequently. We agree with these statements; however, the guidance document should include more information concerning the nature and frequency of the updating process, such as whether there will be a minimum cycle time for updating, what it will take to resolve an issue, and whether there will be an archive/history that shows the progress of emerging information over time. In addition, we suggest that the Drug Watch posting include information regarding the steps the Agency is taking to assess and address the emerging safety issue, and the estimated timeframe for completion of this assessment.

Due to the nature of some adverse events, and the very low frequency with which they occur, it is possible that an emerging safety issue could be posted to the web page and remain there for months or years without any new information being made available. We suggest that there should be some minimum interval for updating each Drug Watch posting (e.g., 4-6 months), even if the "update" states that no new information has become available. The date of the most recent update should be included in Drug Watch postings. There should also be some criteria for removing a posting after a defined period of time (e.g., one year) if no new definitive data become available to resolve the question of causality or risk. Specific guidelines should be set forth when retracting or discounting what was thought to be an emerging signal.

Similar information should be provided regarding timeframes and criteria for updating the "emerging safety information" section in the Patient Information Sheets described in footnote 5, as well as some detail regarding how FDA will deal with issues related to version control/outdated information. For example, if a consumer printed off a Patient Information Sheet last week, how will they know if the information has changed this week? How will patients be informed when "emerging safety information" is removed from the Patient Information Sheet because of a lack of a causal relationship? We suggest that the Patient Information Sheets should include a standard statement referring the reader to the FDA Drug Watch Web page for the most current information, and that new information on a posted drug should be added to a "Highlights" section on Drug Watch.

B. How will FDA decide which drugs will be included on the Drug Watch?

The criteria for posting information on the Drug Watch web page need to be more explicitly defined. This is particularly important because the information will be posted "before (FDA) has fully determined its significance" (line 65). Given the risk of premature and/or inaccurate posting of information that could lead to confusion among healthcare providers and patients, it is crucial to have clearly defined parameters for the selection of information to be posted, including meaningful quality control measures.

In lines 153-163, FDA outlines the factors that will be used to decide which drug products and information are posted on the Drug Watch web page. These criteria are quite vague, and raise a number of questions, some of which are listed below. Information to address these points should be included in the guidance document.

- It is unclear whether the Drug Watch postings will involve only emerging safety issues that represent serious adverse events (e.g., organ damage, arrhythmias, etc.), or whether any adverse event could be subject to posting. We think that the postings would best serve the public interest if restricted to serious adverse events.
- The first criterion, "Whether new and emerging safety information could significantly affect prescribing decisions or how patients should be monitored" (lines 153-157), is vague with regard to the strength of the information necessary to make such a determination. How many cases will be needed – one, three, some other number?
- How will patient exposure figure into the determination?
- How will the Agency determine whether the emerging safety issue is or is not a class effect?
- The second criterion (lines 158-161) notes that if measures can be taken as a result of providing information which might prevent or mitigate harm, then that information could be included on the Drug Watch. What about information where there is not an associated measure which might be taken? Is that communicated and if so, how?
- How will it be determined that "an unapproved (off-label) use of the drug appears to pose a significant risk to patients"? (lines 162-163)
- Does FDA have any plans to evaluate the effects of Drug Watch postings on the behavior of healthcare providers or patients/consumers?

Lines 167-168 note that before posting information on the Drug Watch web site, the Agency will conduct a "...preliminary analysis to determine that the new safety information is sufficiently credible...". Does the Agency plan to publish any information/guidance regarding the thresholds or criteria that might be used in this determination? Examples of such criteria could include pharmacologic plausibility, similar events observed in clinical trials or included in labeling, events observed with other agents in the same class, etc. We recommend that each Drug Watch listing describe the source of the information on which it is based. We also suggest that FDA include a list of the sources of information in rank order of validity, from higher to lower, and describe why some information is considered better than other information.

We recognize that the Agency wants to act quickly to disseminate important safety information to healthcare providers and patients, and does not want to engage in prolonged negotiations with sponsors before posting information on the Drug Watch web site. However, we feel strongly that sponsors should be consulted at the time FDA is conducting their preliminary analysis, and given a defined period of time (e.g., at least 72 hours) to provide any additional information that may help to clarify the safety signal in question. In this context, sponsors' contributions could include information regarding new adverse event reports that are still in the processing cycle, or knowledge of ongoing or unpublished company or other studies that may further substantiate or refute the issue. Sponsors should also be able to provide additional information about a drug at any time during the period a drug is on the Drug Watch Web to ensure that FDA uses all of the resources at its disposal.

Although the draft document goes to great lengths to describe the complete membership of the Drug Safety Oversight Board (DSOB) that will be responsible for determining which products are posted to the Drug Watch web site, according to MaPP 4151-3, a Drug Watch Subcommittee consisting of the DSOB Chair and no more than five additional members will actually make the decisions regarding addition and deletion of information on the web page. The rationale for delegating such important decisions to a small subcommittee is not evident. Since the emerging safety issues to be placed on the Drug Watch web site involve preliminary information that requires further evaluation and verification, there does not appear to be a compelling reason to rush a posting in advance of full consideration by the DSOB. FDA should consider convening an *ad hoc* meeting of the full DSOB for such decisions if speed is of the essence, rather than having the full Board review decisions of the Subcommittee after the fact. If there is an overriding rationale for having the Subcommittee make decisions regarding Drug Watch postings, rather than the full DSOB, this should be fully described in the guidance document.

C. How will drugs be removed from the Drug Watch?

The wording in this section regarding criteria for removing a product from the Drug Watch web site is highly subjective, and gives little insight into what the criteria will be, and how they will be applied. It seems that the instances where it can be definitively stated that no new safety concern exists will be extremely rare (e.g., proving there is no causal relationship), thereby making removal of a product from the Drug Watch difficult, if not impossible. We recommend that the Agency develop a more specific decision tree for removal or deactivation of Drug Watch listings, and include it in the guidance document. The guidance document should also include information regarding how FDA will communicate the removal of items from the Drug Watch Web site.

As noted in our comments on Section III.A above, the Agency should also establish criteria for removing a product from the Drug Watch web site if no new definitive data become available after a certain period of time (e.g., a year).

Once information about a sponsor's product has been posted, the draft guidance does not include a provision for the sponsor to appeal the decision or to propose alternative wording. A mechanism should be established for the sponsor to request DSOB review, and potentially withdrawal of the posted information, based on criteria demonstrating that the posting was inaccurate or lacked a credible basis. It may also be of value if the Drug Watch web site had a facility to allow sponsors to comment on the posted information, ideally providing the opportunity for a unified and informative approach to both patients and healthcare providers.

Documenting resolution of an emerging safety issue is an important aspect of the process that will reassure the public that issues haven't just disappeared, thereby instilling greater confidence in the program. Therefore, it is important that when a product is removed from the Drug Watch, it be done in a timely manner, and the rationale for removal and information upon which the decision to remove it is made available on the web site, with the same level of highlighting and publicity that the original posting received. This "exonerating information" should remain on the web site for a specified period

of time. We also recommend that the Agency develop and maintain a permanent on-line reference for each issue that is posted to the Drug Watch, including how it was evaluated, and its resolution.

D. Will sponsors be notified that a drug will be placed on the Drug Watch?

FDA indicates that sponsors will be notified "shortly before" the first instance in which information regarding their product is posted on the Drug Watch web site (lines 216-218). Additional clarification regarding the definition of "shortly", the nature of the notification (e.g., will the sponsor merely be told that information will be posted, will the wording of the posting or the data upon which FDA made their determination be provided, etc.) is needed. It is important for sponsors to have timely access to the underlying information, and we recommend that the guidance specifically state that the sponsor notification will identify the source of the information, and that a copy, including any special analyses performed by FDA, will be provided if the sponsor does not already have the relevant information.

In addition, FDA has indicated in other fora that sponsors will not have the opportunity to have input into the decision to post information or the wording to be used in the posting. GSK strongly believes that sponsors should have a reasonable period of advance notification and an opportunity to participate in the decision, due to the potentially significant impact on patient and physician behavior, as well as the potential for inaccurate information to confuse patients and healthcare providers, and to cause irreparable damage to the sponsor. As noted above, sponsors may be able to provide additional information regarding the emerging safety issue, such as new adverse event reports that are still in the processing cycle, or knowledge of ongoing or unpublished company or other studies that may further substantiate or refute the issue. We recommend that a minimum of 72 hours be provided for sponsors to provide additional information to FDA, complete a preliminary evaluation, and confirm that the information is credible, before the drug is posted on the Drug Watch Web page.

This period of time will also allow sponsors to prepare for the announcement of the emerging safety issue on the Drug Watch web site, since the sponsor is one of the main entities to which patients and healthcare providers will turn for information. It is important for FDA to recognize that the Agency also needs to be prepared to handle a significant number of telephone calls and other requests for information about drugs posted on Drug Watch, not only from healthcare providers and the media, but also from patients with varying levels of healthcare literacy.

The guidance states that sponsors will be notified before the **first** instance in which information regarding their product is posted on the Drug Watch web site, which implies that they will not be notified in advance of any subsequent changes or additions. Sponsors should be notified in advance of any and all postings regarding their products, as they will need to be prepared to respond to inquiries from patients, healthcare providers, other regulatory authorities, media, etc. regarding this information.

Sponsor preparation for similar announcements of new safety issues typically includes mass communications to employees, sales forces, and other stakeholders. In addition, Medical Information and Safety departments must anticipate the spectrum of questions that the media and concerned customers will ask immediately following a Drug Watch announcement and must ensure adequate resources are in place to deal with spikes in call volume and adverse event reporting. Health care providers must also be prepared in advance for the increase in calls they will receive from patients. In addition, foreign affiliates must translate the Drug Watch information and be prepared to discuss it with their local regulators and customers. Presenting an intelligent and unified response benefits the image and credibility of sponsors and of the Agency. We encourage FDA to revise this section to recognize that it takes a minimum of 72 hours for companies to make even the most basic preparations for new safety announcements. That timeframe is contingent on the sponsor having complete and ongoing knowledge of the safety issue as it develops.

Another aspect of the notification process that concerns us involves Drug Watch postings for potential class effects, particularly when the adverse event has not been reported with the sponsor's product,

although it is a member of the class. An example of such a situation occurred recently when the Agency decided to require black box warnings for all non-steroidal anti-inflammatory agents (NSAIDs). Sponsors of most NSAIDs were unaware that cardiovascular and dermatologic reactions were "emerging safety issues" for their products, and most were put in the awkward position of explaining the new warnings and their lack of supporting evidence to healthcare providers and patients. The Agency should provide sufficient information and documentation to sponsors of all products in the affected class so that they can adequately explain the situation to their customers, as well as to regulatory authorities in other countries where they may market the product.

E. How will the Drug watch affect the promotion of prescription drugs?

We agree with the position outlined in the draft guidance that information posted on the Drug Watch web site should not be used for promotional purposes, and suggest that the guidance include a specific statement to the effect that information posted on the Drug Watch that is not also mentioned in the label may not be used for promotional purposes, since it is preliminary in nature.

Thank you for your consideration of these comments.

Sincerely,

Cynthia R Engle, for

Edward N. Pattishall, MD, MPH
Vice President
Global Clinical Safety & Pharmacovigilance